REMARKS

Claims 1-14 and 16 are pending. A new claim set is provided above. Changes to the claim set are indicated in the following section entitled "Version Showing Changes Made".

Claim 16 has been added as a claim depending from Claim 1, specifying that the VEGF response is mitogenic activity. Support is found, for example, at page 56, lines 1-14.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 1-3 and 7-14 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action states that the specification, while enabling for substitution with aspartic acid, does not reasonably provide enablement for any amino acid modification as encompassed by the claims. Applicants respectfully traverse.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure . . . coupled with information known in the art without undue experimentation." (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Applicants submit that these requirements are met.

As MPEP § 2164.01 points out, "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (citing *In re Angstad*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)). Applicants submit that the present disclosure, along with the general knowledge in the field, fully enables the skilled artisan to make and use the claimed invention without undue experimentation.

Applicants also point out that one need not provide every imaginable embodiment of an invention to provide enablement. And, the presence of inoperative embodiments does not necessarily render an invention nonenabled (*see* MPEP § 2164.08(b) and cases cited therein).

The number of possible amino acid modifications of cysteine residues in VEGF is not great, such modifications are fully enabled by the specification and well known in the art, and routine screening of proteins for their ability to bind VEGF receptors is well known and is detailed in the specification, as are assays for a VEGF response.

The present disclosure also gives substantial direction as to the importance of the different cysteine residues VEGF in making the claimed variants. The high importance of cysteines at positions 51 and 60 of the VEGF amino acid sequence is repeatedly emphasized.

As an illustration of a determination of undue experimentation, in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), the Federal Circuit stated that:

> "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Id. at 1404.

In In re Wands, the claims were drawn to methods of immunoassay of HBsAg by using high-affinity monoclonal IgM antibodies. The claims were rejected by the Examiner, affirmed by the Board, as requiring undue experimentation in the creation of the monoclonal antibodies. The Federal Circuit reversed, on the basis that the experimentation required was not "undue". The steps for the creation of the monoclonal antibodies, as outlined in by the Federal Circuit, were provided:

a) an animal is immunized with the antigen of choice;
b) after a period of time, the spleen is removed;
c) the lymphocytes are separated from other spleen cells;
d) the lymphocytes are mixed with myeloma cells, and treated to fuse the cells; and

e) hybridoma cells that secrete the desired antibodies must be isolated from the "enormous mixture" of other cells, using a series of screening steps, including
   i) culturing the cells such that only hybridoma cells grow;
   ii) hybridomas are isolated and cloned, by placing single hybridoma cells in separate chambers and growing them;
   iii) the secreted antibodies from each clone are screened to see if they bind to the antigen, a step which frequently requires the screening of "hundreds" of clones.

In the instant case, the steps for identifying a VEGF antagonist are:

a) constructing a vector such as detailed in the present examples;
b) constructing primers for the desired variants;
c) expressing and isolating each variant;
d) testing variants for antagonist activity.

In comparison with the *Wands* procedures, production and activity determination of the claimed VEGF variants is not "undue experimentation".

The basic idea of the present application is to disrupt normal dimerization by rendering the VEGF unable to form normal disulfide bridges at the cysteine residues known to be involved in dimerization. Applicants have shown that such variants can inhibit the activity of native VEGF. There is nothing special about the substitution of aspartic acid for cysteine, this is provided in the application only as an example. Applicants submit that other modifications affecting normal dimerization of VEGF polypeptides will work similarly to the exemplified polypeptides.

The Office Action cites Pötgens (J. Biol. Chem. 269(52):32879-32885(1994) at page 32884) for the premise that "VEGF must dimerize in order to bind to its receptor, and receptor binding is a prerequisite for antagonism". Applicants note that Pötgens describes binding in terms of apparent binding to cells, rather than specific binding to receptors, as is shown in the present disclosure. The receptors for VEGF were just being described around the time of the Pötgens publication, so these investigators did not have a specific assay at

their disposal for receptor binding. The present disclosure shows binding of a monomeric VEGF variant to both the KDS and FLT-1 VEGF receptors, as well as antagonism of VEGF activity (page 54, line 17 to page 56, line 14), revealing that the above premise is not true. Therefore, this application provides the skilled artisan with the expectation that modifications other than those provided in the specific examples will have similar activity. As discussed above, such modifications are taught in the specification and are well within the skill of the ordinary artisan in the field. The conclusion of Pötgens is not consistent with the present results, but is based on a less specific test of receptor binding.

Finally, the Office Action suggests that the application merely provides an invitation to experiment, such as the citation in Pötgens, "A strategy for designing dominant-negative VPF analogues, which dimerize with and inactivate wild-type VPF subunits, may provide a future approach toward VPF inhibition." Applicants submit that, on the contrary, the present application provides specific instruction to obtain a well-defined invention. The claimed variants have modifications to at least one cysteine residue, do not properly dimerize, bind VEGF receptors, do not significantly induce a VEGF response, and inhibit biological activity (induction of a VEGF response) of native VEGF. A working example is provided, as is ample instruction for making and using others. This is not a mere suggestion to investigate.

In view of the discussion above, Applicants submit that Claims 1-3 and 7-14 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, withdrawal of this rejection is respectfully requested.

Applicants submit that the application is in form for allowance and early notification of such is requested. If there are remaining issues which the Examiner believes may be resolved by telephone, she is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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VERSION SHOWING CHANGES MADE

Please enter the following new claim:

--16. The antagonist molecule according to Claim 1 wherein said VEGF response is mitogenic activity.--